Applicant: Alnylam Europe AG

Serial No.: Not Yet Assigned

Attorney's Docket No.:

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Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1-85 (Canceled)

- 86. (New) A double-stranded ribonucleic acid (dsRNA) having a strand S1 which is complementary at least in segments to a target gene (the antisense strand), a strand S2 which is at least substantially complementary to the strand S1 (the sense strand), wherein the dsRNA is capable of inhibiting the expression of the target gene upon introduction into a cell expressing said target gene, and wherein at least one lipophilic group is linked only to the strand S1, or only to the strand S2.
- 87. (New) The dsRNA of claim 86, wherein the link between the lipophilic group and the dsRNA strand is a covalent bond.
- 88. (New) The dsRNA of claim 87, wherein the lipophilic group is covalently attached to a 5'-end of the strand S1 or a 5'-end of the strand S2.
- 89. (New) The dsRNA of claim 87, wherein the linkage between the lipophilic group and the dsRNA strand comprises a phosphodiester group.
- 90. (New) The dsRNA of claim 87, wherein the linkage between the lipophilic group and the dsRNA strand does not comprise a phosphodiester group.
- 91. (New) The dsRNA of claim 88, wherein the lipophilic group is covalently attached to the 5'-end of the strand S1.
- 92. (New) The dsRNA of claim 88, wherein the lipophilic group is covalently attached to the 5'-end of the strand S2.

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93. (New) The dsRNA of claim 86, wherein the dsRNA is between 16 and 30 nucleotides in length.

- 94. (New) The dsRNA of claim 86, wherein the lipophilic group is a steroid or a branched aliphatic hydrocarbon, or a combination thereof.
- 95. (New) The dsRNA of claim 94, wherein the lipophilic group is a sterol.
- 96. (New) The dsRNA of claim 95, wherein the sterol is cholesterol or a cholesterol derivative.
- 97. (New) The dsRNA of claim 96, wherein the lipophilic group is cholesteryl (6-hydroxyhexyl) carbamate
- 98. (New) The dsRNA of claim 86, wherein the lipophilic group is 12-hydroxydodecanoic acid bisdecylamide.
- 99. (New) The dsRNA of claim 86, wherein the target gene is a viral gene.
- 100. (New) The dsRNA of claim 86, wherein the lipophilic group has a logK_{ow} exceeding 2.
- 101. (New) The dsRNA of claim 86, wherein the lipophilic group has a $logK_{ow}$ exceeding 3.
- 102. (New) The dsRNA of claim 86, wherein the lipophilic group has a logK_{ow} exceeding 5.
- 103. (New) A pharmaceutical composition for inhibiting the expression of a target gene in a mammal, comprising:
- a. a double-stranded ribonucleic acid (dsRNA) having a strand S1 which is complementary at least in segments to a target gene (the antisense strand), a strand S2

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which is at least substantially complementary to the strand S1 (the sense strand), wherein the dsRNA is capable of inhibiting the expression of the target gene upon introduction into a cell expressing said target gene, and wherein at least one lipophilic group is linked only to the strand S1, or only to the strand S2; and

b. a pharmaceutically acceptable carrier.

104. (New) The pharmaceutical composition of claim 103, wherein the pharmaceutically acceptable carrier is an aqueous solution.

105. (New) The pharmaceutical composition of claim 103, wherein the pharmaceutically acceptable carrier does not contain an agent that mediates the uptake of the dsRNA into a cell.

106. (New) A method for inhibiting the expression of a target gene in a mammal, which comprises administering a pharmaceutical composition comprising a double-stranded ribonucleic acid (dsRNA) and a pharmaceutically acceptable carrier, wherein the dsRNA comprises a strand S1 which is complementary at least in segments to a target gene (the antisense strand), a strand S2 which is at least substantially complementary to the strand S1 (the sense strand), wherein the dsRNA is capable of inhibiting the expression of the target gene upon introduction into a cell expressing said target gene, and wherein at least one lipophilic group is linked only to the strand S1, or only to the strand S2.

107. (New) A method for making a double-stranded ribonucleic acid (dsRNA), comprising the steps of:

- a. preparing a first RNA strand S1 and a second RNA strand S2, wherein strand S1 is complementary at least in segments to a target gene, strand S2 is at least substantially complementary to the strand S1, wherein the dsRNA is capable of inhibiting the expression of the target gene upon introduction into a cell expressing said target gene, and wherein at least one lipophilic group is linked only to the strand S1, or only to the strand S2; and
- b. mixing strand S1 and strand S2 to form a dsRNA.

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108. (New) The method of claim 107, further comprising the step of attaching the lipophilic group to strand S1 or strand S2, wherein the step comprises reacting a lipophilic molecule having a phosphoramidite group with a 5'-hydroxyl group of strand S1 or strand S2.

109. (New) The method of claim 108, wherein the lipophilic molecule having a phosphoramidite group is cholesteryl N-[6-(2-cyanoethoxy)-N,N-diisopropylaminophosphanyloxy]-hexyl carbamate or 12-[(2-cyanoethoxy) -N,N-diisopropylamino-phosphanyloxy]dodecanoic acid bisdecylamide.